Predicting individual radiation sensitivity:
Individual radiation sensitivity in the context of radiological emergencies

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Outline

- General issues to consider
- Background of IND event and response
- Assessing exposure
- Medical countermeasure “threat space”
- Protector, Mitigator*, Treatment
- Consideration of issues of “an assay”- uncertainties, how “good” must it be & cost
- How “an assay” may be useful
- How the genetic information might be used
- Summary (revised at end of meeting)

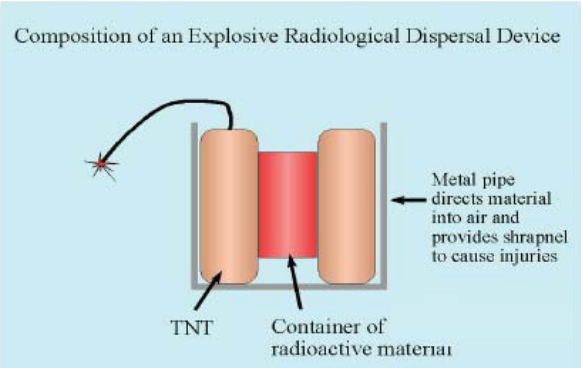
Issues to consider

- Distinguishing needs for
  - clinical radiation therapy
  - managing acute radiation syndrome (ARS) and delayed effect of acute radiation injury (DEARE)
  - surveillance for radiation-induced carcinogenesis
- Populations at risk
  - External irradiation versus internal contamination
  - Normal tissue injury- lung (high dose);
  - Combined injury: trauma plus radiation
  - Carcinogenesis
- So many uncertainties!!
- How good is the test
- Financial considerations
- What difference does it really make?

RDD and RED

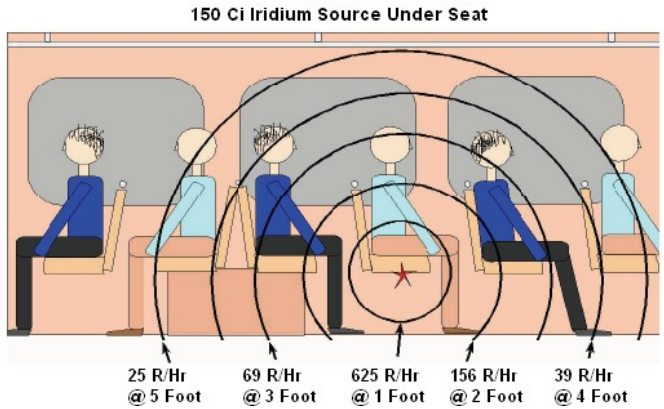
Radiological Dispersal Device (RDD)

Explosive



Non-explosive

Radiological Exposure Device (RED)



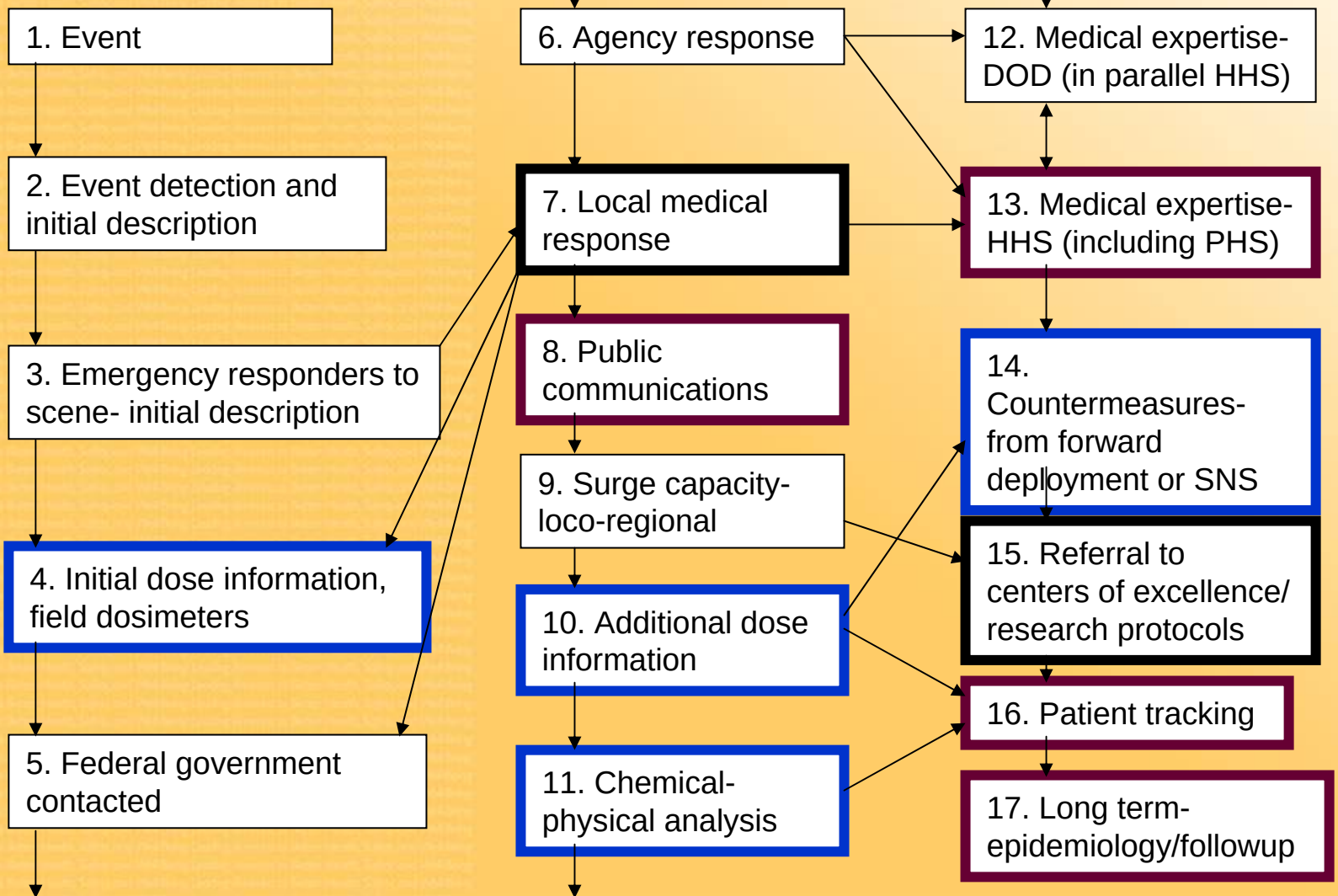
Chain of Medical Response

For publication- do not circulate

Rad- Lab Network Analytical

Medical- Victim management

Both



Industrial, other
HHS may be involved

EVENT

IND- large mass casualty

RDD- explosive

RDD- non-explosive
Air, food, water, soil

RED- exposure

Features
- Immediately recognizable as “an event”
- Radiation might not be detected immediately
- Health physicists must determine time/dose in various zones due to radiation
- Casualties from IED immediate
- No immediate death from radiation but victim decontamination essential
- Life saving may be performed before decon, if necessary.

Features
- Time of initiation of release may not be known.
- Can be mass casualty in ventilation or food/water.
- Radiation dose can cause death in some scenarios
- Health physics critical for detection and monitoring
- May require broad interdiction of food, water until details sorted out

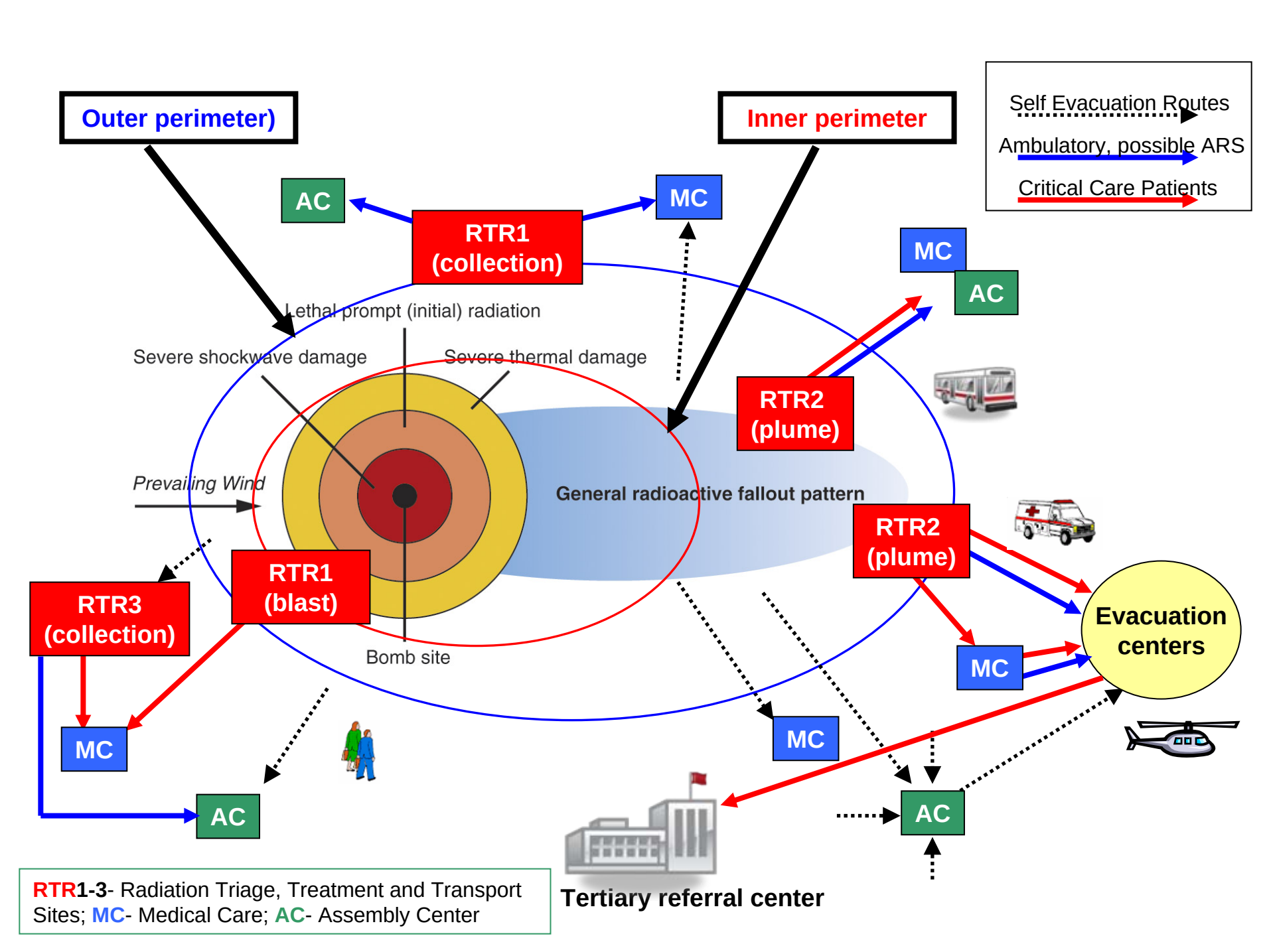
Features
- Time of initiation of exposure may not be known.
- Risk of mass casualty low
- Likely only partial body dose so radiation-related death would be low.
- May be difficult or impossible to sort out who was exposed to low doses

Long term monitoring may be required for victims and responders.

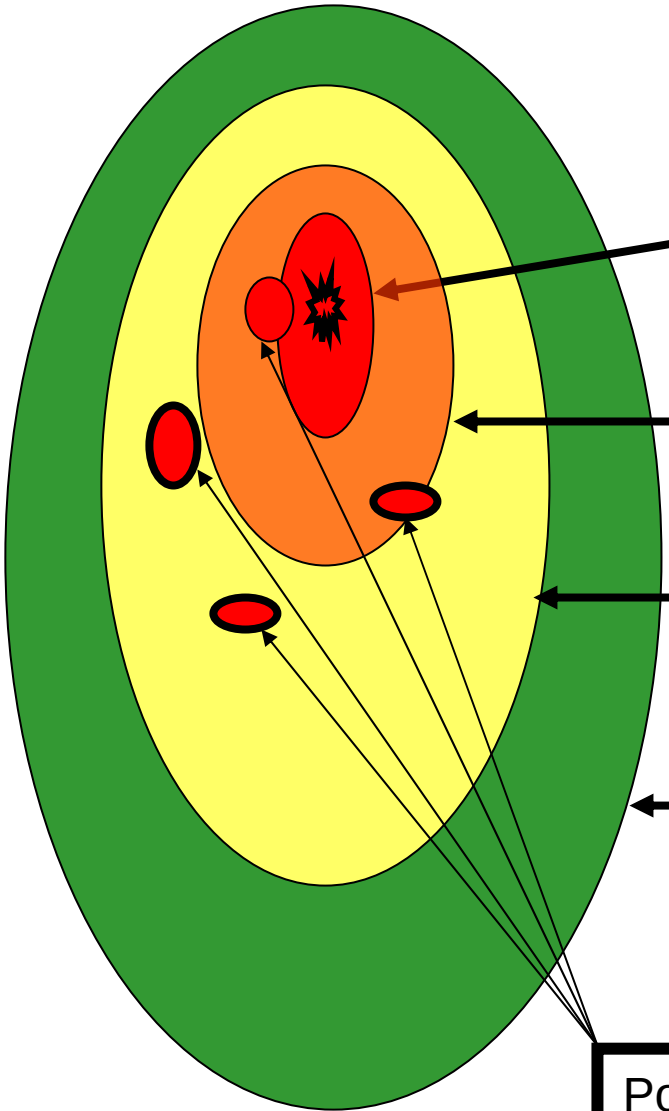
Detonation Casualties

Used for an example

Doses in Rem or cSv	*1-KT*	*10-KT*
Prompt fatalities:	**> 7K**	**> 13K**
Expectant (> 830):	**~ 18K**	**~ 114K**
Intensive care (IC) ward (530-830):	**~ 19K**	**~ 90K**
IC/minimum care ward (300-530):	**~ 33K**	**~ 141K**
Minimum care ward (150-300):	**~ 66K**	**~ 150K**
Outpatient (70-150):	**~ 83K**	**~ 159K**
Health monitoring (25-70):	**~ 106K**	**~ 128K**
Worried well (< 25):	**> 150K**	**> 212K**


Outer perimeter)
Inner perimeter
Self Evacuation Routes
Ambulatory, possible ARS
Critical Care Patients
AC
MC
RTR1 (collection)
MC
AC
Lethal prompt (initial) radiation
Severe shockwave damage
Severe thermal damage
RTR2 (plume)
Prevailing Wind
General radioactive fallout pattern
RTR2 (plume)
RTR3 (collection)
RTR1 (blast)
Bomb site
Evacuation centers
MC
MC
MC
AC
AC
Tertiary referral center
RTR1-3- Radiation Triage, Treatment and Transport Sites; MC- Medical Care; AC- Assembly Center

Zones: How time within inner, outer and intermediate zones can be determined



10 rem/hr X 0.5 hr = 5 rem

10 rem/hr X 2.5 hr = 25 rem

1 rem/hr X 5 hr = 5 rem

"inner zone"

0.1 rem/hr X 50 hr = 5 rem

"intermediate zone"

0.01 rem/hr X 500 hr = 5 rem

"outer zone"

Potential local "hot spots" from debris and fall out

Radiation Syndromes: Management depends on dose!

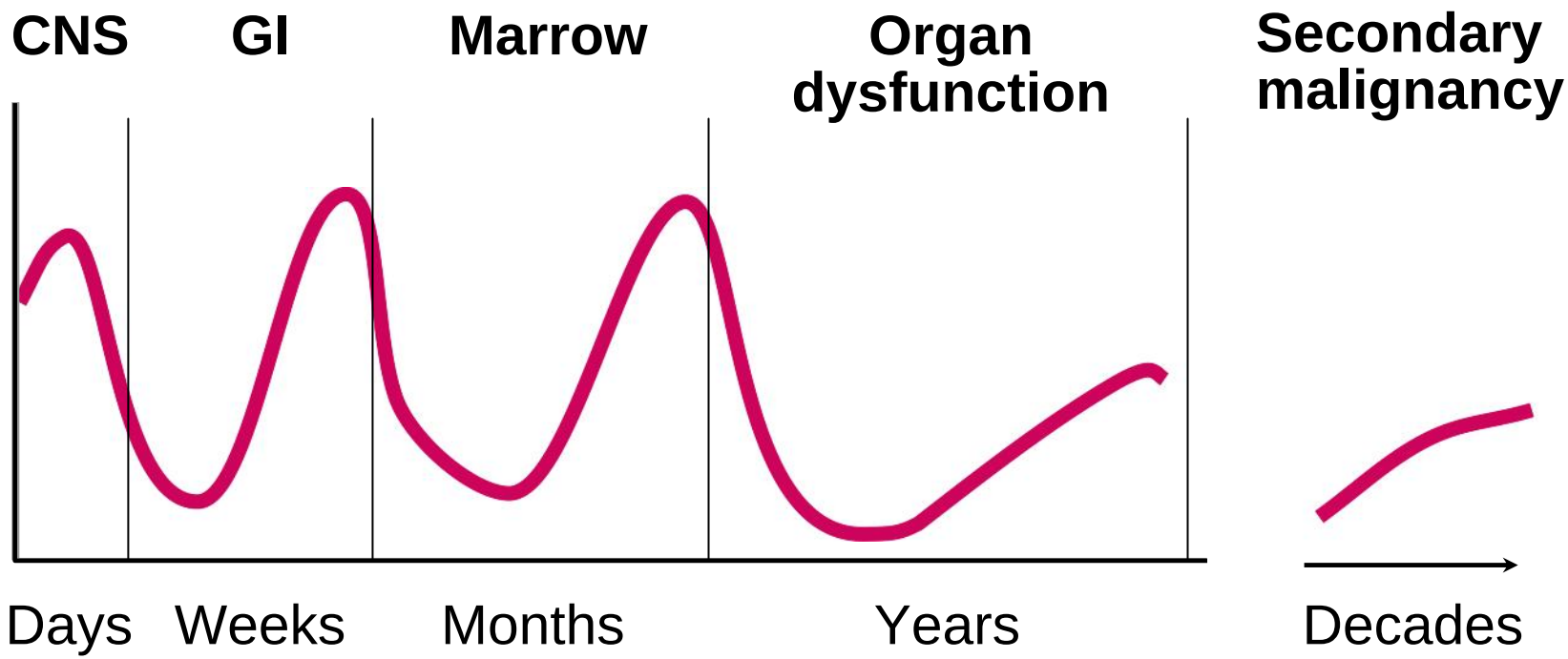
- **Acute Radiation Syndrome (ARS) and Delayed Effect of Acute Radiation Exposure (DEARE)**
  - **Continuum of injuries**
  - **Time to clinical manifestation depends on organ system and dose**
  - **Different organ systems have different "incubation periods"**

Hematological syndrome (>2 *Gy)	**few days to 2 months**
Gastrointestinal syndrome (>6 Gy)	**few days to a week**
CNS/Cardiovascular syndrome (>10 Gy)	**immediate**
Cutaneous syndrome	**few days to weeks**

- **Combined injury (early intervention required)** **immediate**
- **Phases: Prodrome → Latent → Manifest**

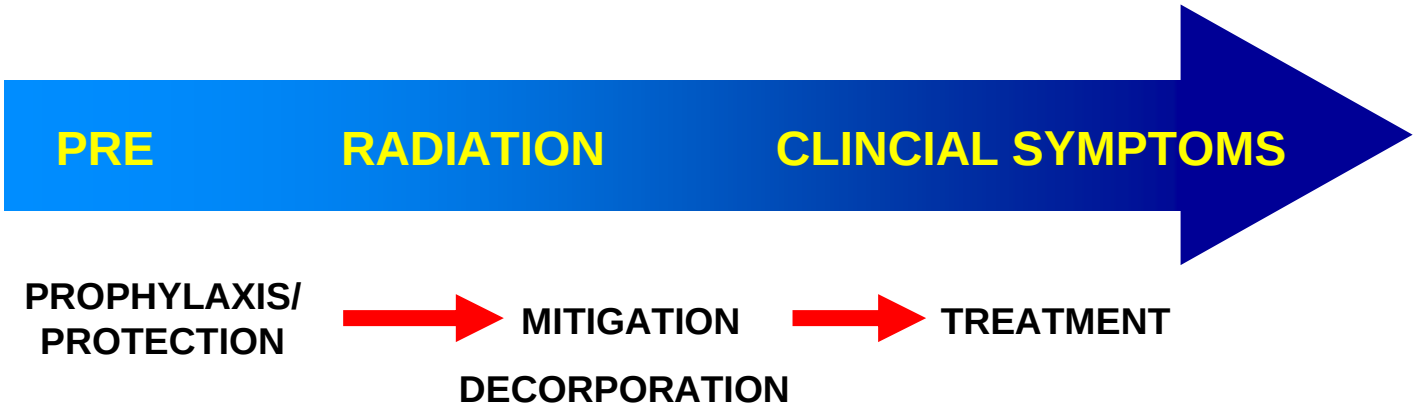
***1 Gy = 100 rads (or approx. 100 rem)**

Time Course for Radiation Effects and Timing for Medical Countermeasures



Critical question: can we intervene effectively post-exposure?

Definition of Medical countermeasures (MCM)



Some questions regarding individual sensitivity:

Who needs medical intervention?

How quickly can you tell?

What tests are needed and what is feasible in the CONOPS?

Can information impact use of resources/personnel?

How much will this improve on “empiricism”?

Assessing exposure and contamination conceptual approach In addition to medical history

Event	Radio-bioassay (analyze the radionuclide)	Triage by hematology	"Rapid" biodosimetry (molecular) in development	Cytogenetics (dicentrics)
RDD, explosive	+ + + +	+	+ +	+ + +
RDD, non-explosive	+ + + +	+	+ +	+ + +
RED	+	+ +	+ + +	+ +
IND	+ + +	+ + + +	+ + + +	+ + + +
Concerned citizens or uncertain history	+ + + +	+	+ + +	+ +

Expertise required for comprehensive medical response to radiation event

Molecular & cellular biology → Tissue & organ biology → Damage repair & inflammation → Medical countermeasure (*NIAID, BARDA, DOD*) / Medical management → REMM *(NLM/HHS)*

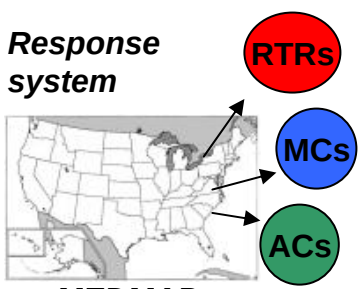
Basic science

Applied science & medical experience

Rad LN

Triage → Transportation → Fatality management / Medical expert care → Long term management

Response system



MEDMAP

Local, regional and national through Regional Emergency Coordinators

Radiation Injury Treatment Network (RITN); & NDMS

REMM

Epidemiology

PAGs for site restoration

International partners

Topics of this conference

- Genetic predisposition for radiation associated cancer
- Candidate genes
- Genome-wide approaches (SNPs, others?)
- Bioinformatics
- High-throughput devices
- What next?

Considerations for the assay (1): so many uncertainties!!

- Exposure- how accurate will this be?
- Contamination- external; internal
- Dose: low- ?adaptive; IND pulse-instant; external material: dose-rate effect
- RBE of neutrons
- Heterogeneity- partial shielding
- DMF- tissue specific mechanism?
- Assay- time and expense- for use in large group for triage or in detailed risk analysis?
- Single or multiple assay- gene, proteins?
  - Pre or post RT

Considerations (2)- how to use the test?

- Intervention- selecting “at risk” groups for the assay?
- How big a subset(s) is identified?
- Validating effect of “susceptibility” and intervention (does the test provide useful information)? And what will be done about it?
- Offering assurance to victims? How to factor in other lifetime cancer risks?
- Given all the physical and medical variables and how big a DMF or hazard function is worth detecting- 1.2, 1.5, 2, 5, 10 ?

Considerations (3)- cost?

- How much will it cost?
- Could the test have an indication in routine practice (“dual use”- radiation oncology or “life” risk analysis) or will use only for terrorism event justify expense? If it is $1 vs 100 vs 1000 it will matter.
- What does a positive test cost for those with it and what does it save for those without it? What frequency of positivity is needed to make it worth doing 1/100, 1/10 to save healthcare expenses?

How “good” are some current tests (1)

- Breast cancer- gene profiles and risk groups
- Prostate cancer- SNPs to predict risk
- Lung cancer promoter methylation
- “Drug” metabolism polymorphisms?
- Are there “populations” with some clustering of genetic changes that at higher risk, e.g. BRCA1 and 2?
- Pre- versus post-RT exposure profile (in vitro or post-event)?

How “good” are some current tests (2)

Breast cancer- gene profiles and risk groups

- Oncotype Dx (21 genes)
- Mammaprint (70 genes)
- H/I (2 genes)

Hazard rates for predicting (low versus high risk) for recurrence @ 10 yr ~1.5 – 3

Marchionni L. Ann Int Med 2008, 148:358-369

How “good” are some current tests (3)

- Prostate cancer- SNPs to predict risk
- 5 loci for SNPs (function not known)

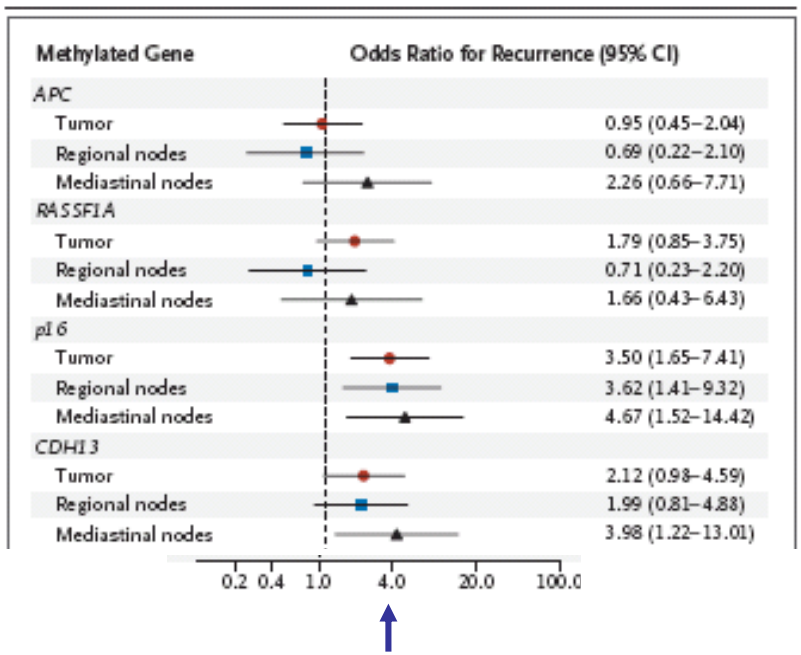
Variable	Case Subjects	Control Subjects	Regression Coefficient	Odds Ratio (95% CI)	P Value†
	no. of subjects (%)				
No. of associated genotypes¶					
0	162 (5.6)	173 (10.1)	NA	1.00	
1	883 (30.8)	631 (36.8)	0.41	1.50 (1.18–1.92)	9.46×10^{-4}
2	1123 (39.1)	618 (36.0)	0.67	1.96 (1.54–2.49)	4.19×10^{-8}
3	548 (19.1)	255 (14.9)	0.79	2.21 (1.70–2.89)	4.33×10^{-9}
≥4	154 (5.4)	38 (2.2)	1.5	4.47 (2.93–6.80)	1.20×10^{-13}

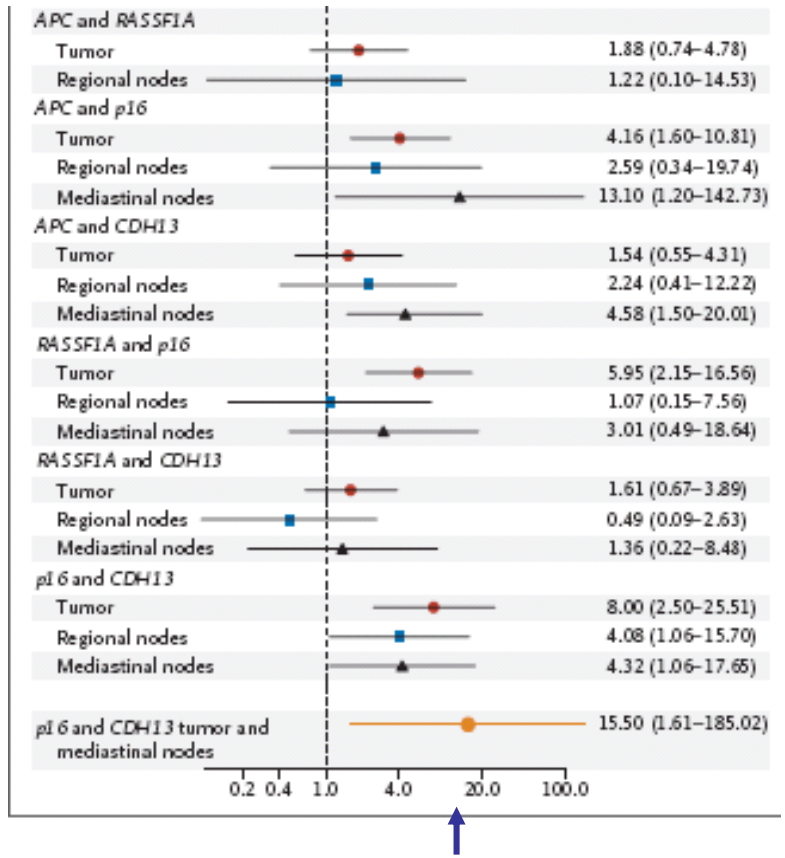
HR: ~1.5 - 4

Zheng SL, N Eng J Med, 2008, 358:910-9

How “good” are some current tests (4a)

Lung cancer, 5 silenced genes felt to be involved in biology of lung cancer



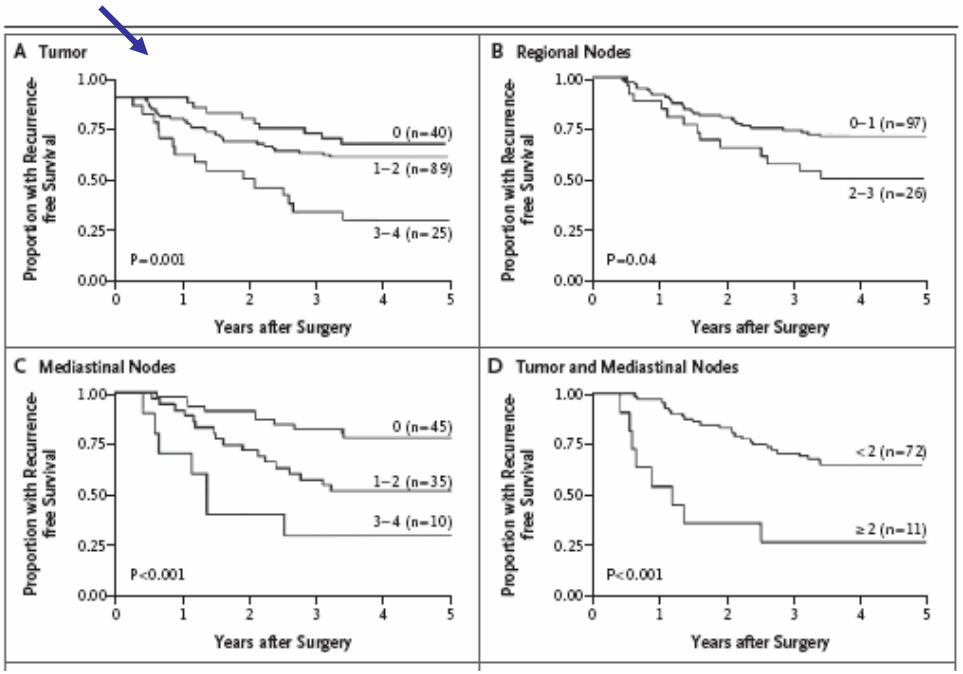


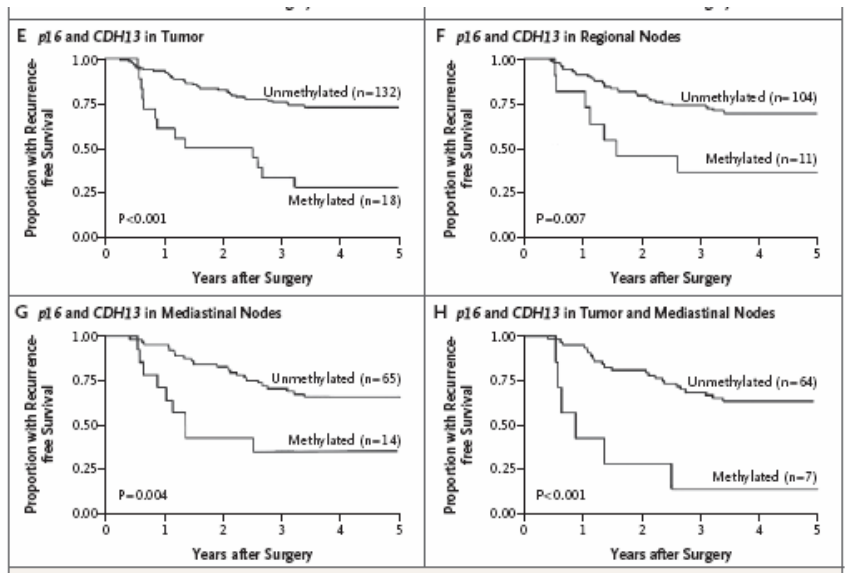
HR: ~1.5 -4 per gene

Up to 15 for doublet

Brock MV, N Eng J Med, 2008, 358:1119-28

How “good” are some current tests (4b)





Brock MV, N Eng J Med, 2008, 358:1119-28

How “good” are some current tests (5)

“Drug” metabolism polymorphisms?

- Response of warfarin during initial anticoagulation
- Cytochrome P-450 genotypes (CYP2C9*1, *2, *3)
- Vitamin K epoxide reductase (VKORC1 haplotypes A and non-A)

Unadjusted hazard ratio for excessive anticoagulation (initial 28 days and longer term) ~1.1 to 2.5 (some significant p values)

Schwarz UI, N Eng J Med, 2008, 358:999-1008

Scenarios and utility of radiation sensitivity (1)

Radiation	Dose range	Effect of concern	Uncertainty	Utility
High dose external beam	Close to organ tolerance (organ dependent)	Enhanced late effect	Dose actually delivered; Volume effects; DMF (Dose modifying factor)	Reduce dose and/or volume; Radioprotector or mitigator
Improvised nuclear device (IND)	~7-8 Gy	ARS- heme, GI, DEARE- lung	Dose heterogeneity; RBE (Relative biological effectiveness), n	BM Tx? or other stem cells; Anti-fibrosis Rx?
IND	2-6 Gy +/- combined injury	ARS- heme, Skin	Dose heterogeneity; RBE	Anticipate ARS; Different burn/skin Rx?

Scenarios and utility of radiation sensitivity (2)

Radiation	Dose range	Effect of concern	Uncertainty	Utility
Radiological Dispersal Device (RDD)- external contamination (also IND fallout)	2-6 Gy	ARS-heme	Dose rate effect	Anticipate ARS or mitigate
RDD- internal contamination	? > 10 ALI (annual limits of intake)	Radiation-induced cancer	Isotope distribution; Committed dose	Decorporation; Surveillance; Chemoprev-ention; Life style intervention
Radiation onc or Diagnostic exams	? cumulative dose > 100 rem?	Radiation-induced cancer	Dose per “hit”	Surveillance; Chemoprevent; Limits to future rad Dx tests?

Who cares about this information?

Who caRO1es?

- **science and new knowledge** are always good, at least for ~15% of applicants; Can't argue (too much) against knowledge.

Who caRxes?

- **for victim-** what can be done with the information; will there be useful intervention/remedy or just more anxiety?
- **for radiation oncology patient-** will treatment change and will dose reduction hurt tumor control (tissue vs tumor DMF?)

Who care$?

-**for healthcare system-** is the test of value- is it cost effective in terms of predictability and useful intervention?

Who cHIPPAres

-**general citizen-** will this information be a part of a pre-existing personalized medicine data base and need to be HIPPA-ized or of concern for job discrimination (susceptibility to radiation or environmental stress)

Issues to consider- for SNPs, CNVs, etc.

- Manage ARS, DEARE; chronic/late effects; or surveillance for radiation-induced carcinogenesis? Are separate tests needed? Will these be organ-specific, too?

- Is what is useful for clinical radiation therapy useful for terrorism;
  - If so at what dose (high, med, low, very low) and which outcome

- Populations at risk- who needs test, beyond routine “clinical Dx” and biodosimetery/radiobioassay (Rad-LN) (Does biodosimetry include [subsume] the individual susceptibility?)
  - External irradiation versus internal contamination
  - Normal tissue injury- which organ systems are at risk
  - Carcinogenesis
  - What is baseline risk that is being increased?

- How does one overlay the test result with the many uncertainties of the event?
  - Physics of IND, radiobiology (RBE), heterogeneous exposure; dose rate

- How do we validate the accuracy of a marker and *then* how do we design and evaluate a medical intervention (mitigate, treat, monitor?)
- Where in the process of having a clinical diagnostic is the current science and methodology?
  - Are we still in the discovery mode?

- How good is the test?
  - Reproducible, rapid (enough),
  - What is the baseline risk? And prevalence of the characteristic/SNP?
  - What is increased risk- DMF, hazard rate, actuarial risk- that should be required or useful? 2 fold increase a minimum?
  - Is there a best test or is a set of tests needed? And can they be done as part of a “package” or at least logical sequence?
  - Automatable?

- Financial considerations
  - Cost of test- what is it likely to be
  - cost of care (saving) could offset cost of a diagnostic if it is pivotal in clinical decision making and identifies reasonable percentage of victims

- What’s next?
  - SNP consortium will happen
  - ? Discovery of underlying biology
  - ? Empirical test that provides useful information